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Plasma Vitamin and Mineral Status in Home Parenteral Nutrition Patients

T. DAVIS, PH.D.,* F. PERRY FRANZ, M.D.,* DEBRA A. COURTNAY, R.N.,* DUANE E. ULLREY, PH.D.,† DONALD J. SCHOLTEN, M.D.,* AND RICHARD E. DEAN, M.D.*

*From the *Departments of Surgery, Michigan State University and Butterworth Hospital, Grand Rapids, and the †Department of Animal Science, Michigan State University, East Lansing, Michigan*

ABSTRACT. Home parenteral nutrition (HPN) provides long-term nutritional support for persons whose absorptive capacity is compromised by a variety of intestinal malabsorption problems. However, the presence of vitamin and mineral deficiency syndromes that normally would not have time to develop in the hospitalized patient receiving total parenteral nutrition has been reported in patients receiving HPN. This study entails a longitudinal survey of plasma concentrations of vitamins A, E, and 1,25-dihydroxyvitamin D, as well as the minerals zinc, copper, and selenium, in patients receiving HPN. Plasma samples from eight patients who had been on HPN for 1–92 months before the study began were obtained once a month over a 12-month period. The blood was drawn immediately before their evening infusion of TPN in order to approximate fasting plasma nutrient concentrations. Patient values were compared to fasting control values and to published norms. Values for vitamin A, 1,25-dihydroxyvitamin D, and zinc all were within the normal range, and there was no evidence of metabolic bone disease. Plasma vitamin E and copper concentrations exceeded the normal range for most of the 12-month period. Of all of the nutrients studied, only plasma selenium concentrations were consistently in the low-normal to below-normal range. Selenium levels in patients on HPN should be monitored regularly, and supplementation may be necessary if clinical conditions warrant. (*Journal of Parenteral and Enteral Nutrition* 11:480–485, 1987)

The use of hyperalimentation to provide nutritional support for malnourished patients has developed from a theoretical concept into standard hospital practice over the past 20 yr.[1,2] This methodology has been combined with procedures used for home hemodialysis and adapted to provide a program for long-term parenteral nutrition which is self-administered in the home.[3–7] Home parenteral nutrition (HPN) is now accepted as standard therapy for selected patients with malabsorption disorders and short gut syndrome.

The use of long-term parenteral nutrition has been associated with some unusual problems. Deficiency syndromes have been described for zinc,[8] selenium,[9] vitamin A,[10] copper,[11] and vitamin E,[12] among others. Metabolic bone disease that may be related to excessive amounts of vitamin D also has been identified.[13,14] In most cases, the symptoms suggestive of these syndromes have developed after several months of HPN. The highly purified nature of the parenteral solutions is largely responsible for these deficiencies, although some have resulted from the infusion of nutrient-deficient solutions. In one case,[10] a vitamin A deficiency was identified, even though retinol had been added to the solution. Retinol was thought to be adhering to the solution container, and oxidizing during storage.

It is of prime importance, therefore, to determine the nutritional status of people using HPN, and to relate their nutritional status to length of time on HPN. The purpose of this study was to compare the status of vitamins A, E, and 1,25-dihydroxyvitamin D and the minerals zinc, copper, and selenium in patients on HPN to controls over a 1-yr period.

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Reprint requests: Alan T. Davis, Ph.D., Director, Nutrition Research Laboratory, Butterworth Hospital, 100 Michigan Street, N.E., Grand Rapids, MI 49503.

MATERIALS AND METHODS

Eight adult patients receiving HPN due to extensive small bowel resections were studied (Table I). All patients received a standard regimen of vitamin and mineral supplementation daily (Table II). Six healthy volunteers (three males and three females) served as controls.

Over a 12-month period, 10-ml samples of blood were drawn monthly from each patient during routine clinic visits. The samples were taken in the late afternoon before the evening TPN infusion in order to approximate a fasting level. The blood was placed in heparinized tubes, placed on ice for 1 hr, and then spun at 800 × *g* for 10 min to separate the plasma from the red blood cells. The plasma was harvested, and frozen at −20°C until analysis. Ten millimeter samples of blood were also drawn from six control subjects once a month for 3 months. The samples were taken at 8 am, after an overnight fast.

Retinol and α-tocopherol were assayed by the method of Bieri et al.[16] The 1,25-dihydroxyvitamin D was assayed with materials obtained from Immuno Nuclear Corporation (Stillwater, MN). Zinc and copper were analyzed by atomic absorption spectrophotometry, via methodologies supplied by Instrumentation Laboratory, using the IL 453 (Lexington, MA). Selenium was measured by the method of Whetter and Ullrey.[21] The data were analyzed

TABLE I
Patient data

Patient no.	Age* (yr)	Indication for HPN	Months on HPN*
1	57	Short bowel syndrome	92
2	64	Short bowel syndrome	56
3	54	Crohn's disease	22
4	64	Crohn's disease	11
5	50	Short bowel syndrome	5
6	36	Short bowel syndrome	1
7	53	Short bowel syndrome	1
8	24	Short bowel syndrome	1

* At the start of the study.

TABLE II
Standard regimen of vitamin and micronutrient supplementation

Nutrient	Amount provided per day
Vitamin A (as retinol)	2300 IU*
Vitamin D_2 (as ergocalciferol)	200 IU*
Vitamin E (*d-α*-tocopherol acetate)	10 IU*
Zinc (as $ZnSO_4 \cdot 7H_2O$)	5 mg†
Copper (as $CuSO_4 \cdot 5H_2O$)	1 mg†

* MVI-12, Armour, Kankakee, IL.
† SoloPak, Franklin Park, IL.

via analysis of variance,[17] which allowed for missing data.[18] Linear regression equations of months on HPN prior to the start of the study *vs* plasma vitamin concentration were calculated, along with correlation coefficients.[17]

RESULTS

The data are shown in Figures 1–6. Normal ranges for plasma vitamin and mineral levels are shown as dashed lines on each figure.[19] Figure 1 shows that mean values for plasma vitamin A in patients ranged from 45.5 to 58.8 μg retinol/dl. Control values were 28.9 ± 3.6 μg/dl (mean ± SEM). All mean values were within the normal range. When plotted as months on HPN prior to the start of the study *vs* mean retinol concentrations, the linear correlation coefficient was 0.13 (not significant).

Vitamin E data are shown in Figure 2. The control values were 1.8 ± 0.3 mg/dl, which was within the normal range. Mean values for the patient group generally exceeded normal values. The linear correlation coefficient ($r = 0.90$) indicated significant correlation between time on HPN and plasma vitamin E concentration. The vitamin E distribution by month was also marked by high

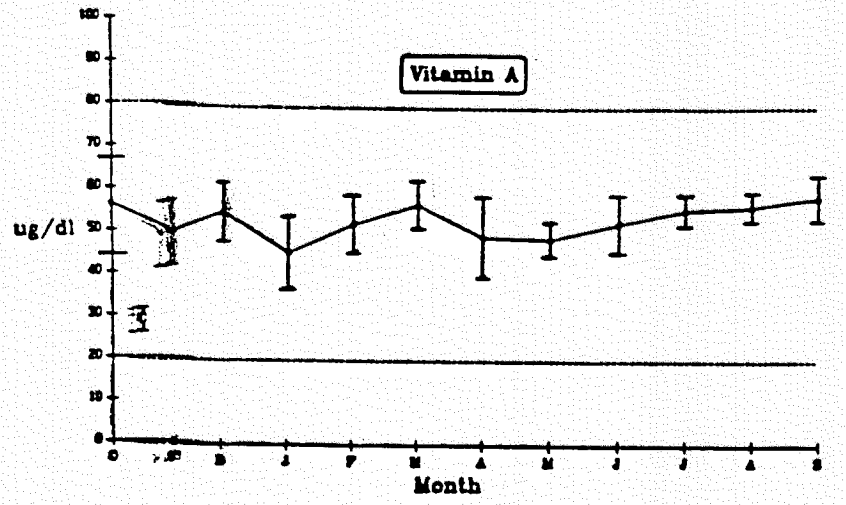

FIG. 1. Plasma levels of vitamin A (retinol) in subjects on HPN. Values were obtained once a month over a 12-month period. The normal range is indicated by two dashed lines. Control values are indicated by the open circle with error bars. Control and patient values are listed as mean ± SEM.

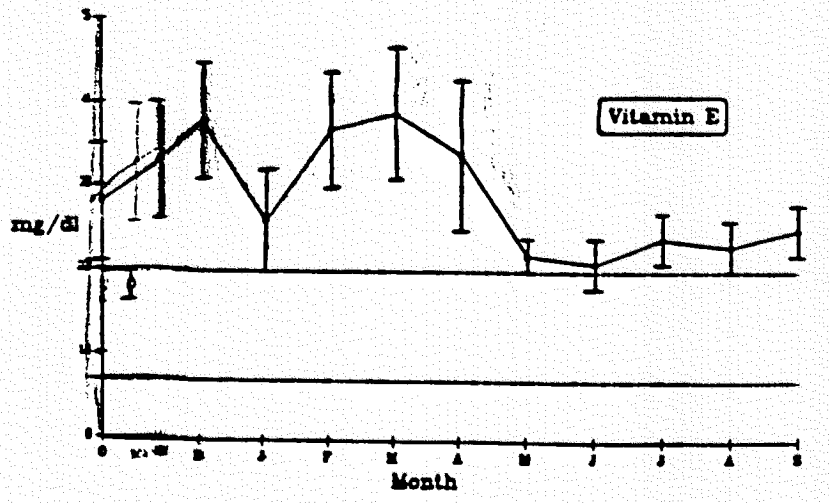

FIG. 2. Plasma levels of vitamin E (*d-α*-tocopherol) in patients on HPN. Data presented are as described in Figure 1.

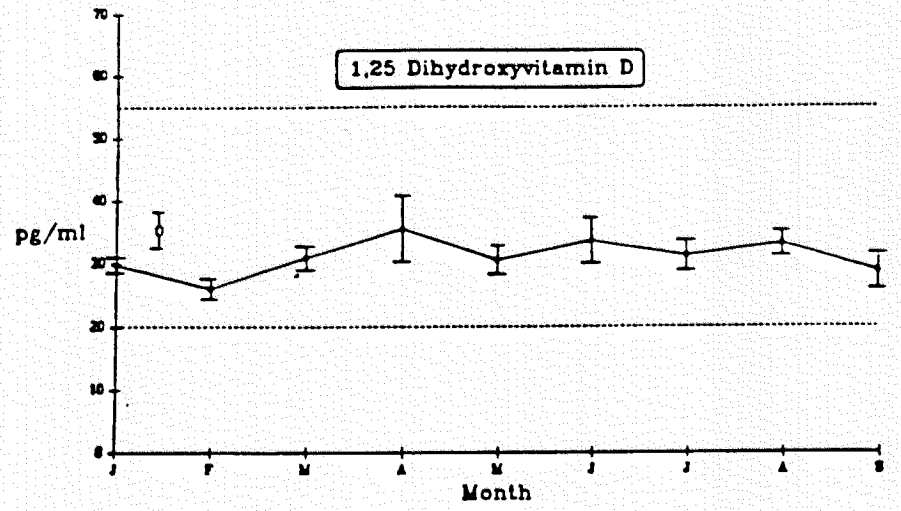

FIG. 3. Plasma levels of 1,25-dihydroxyvitamin D in patients on HPN. Data presented are as described in Figure 1.

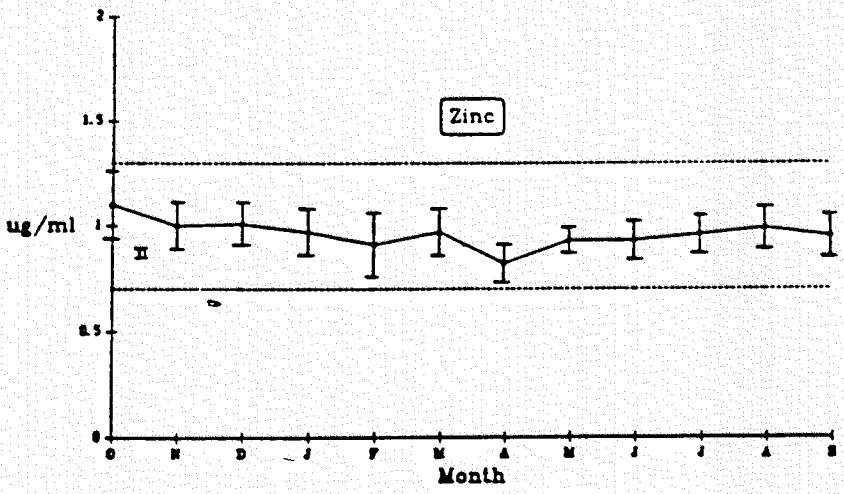

FIG. 4. Plasma levels of zinc in patients on HPN. Data presented are as described in Figure 1.

variability during the first 7 months of the study, which was largely due to two patients who had fluctuating results ranging from 1.5 to 7.3 mg/dl.

Values for 1,25-dihydroxyvitamin D are shown in Figure 3, with means for patients and controls (35.3 ± 2.9 pg/ml), all within the normal range. No correlation between time on HPN and dihydroxyvitamin D concentration was seen. The correlation coefficient for the linear fit was −0.30.

The mean values for plasma zinc concentrations in patients and controls (0.87 ± 0.02 μg/ml) were within the normal range (Fig. 4). Patient values showed little variability over the 12-month period, ranging from a mean of 1.10 ± 0.16 in October to a mean of 0.82 ± 0.90 in April. No correlation between time on HPN and zinc concentrations was seen using linear regression (r = 0.47).

Values for plasma copper concentrations are shown in Figure 5. Patient values were at the upward end of the normal range, and frequently exceeded this range. Mean patient values ranged from 1.35 ± 0.25 μg/ml in September to 1.79 ± 0.33 μg/ml in April. The controls also exceeded the normal range (1.9 ± 0.2 μg copper/ml plasma). Length of time on HPN and copper concentrations were significantly correlated using linear regression (r = −0.75).

Selenium concentrations are depicted in Figure 6. Selenium values for patients tended to be toward the low end of the normal range; several patients had values below normal. The controls had plasma selenium concentrations of 0.122 ± 0.006 μg/ml, which was approximately the midpoint of the normal range. No significant correlation was seen between time on HPN and plasma selenium concentrations by linear regression (r = 0.26).

DISCUSSION

The advent of home parenteral nutrition (HPN) has allowed greater flexibility and success rates for physicians treating patients with a variety of disease states. HPN has been commonly used in the management of enterocutaneous fistulas and as an adjunct to cancer therapy. Perhaps its greatest use has been in the treatment of patients with Crohn's disease who have had multiple small bowel resections resulting in short gut syndrome. There are numerous patients whose continu-

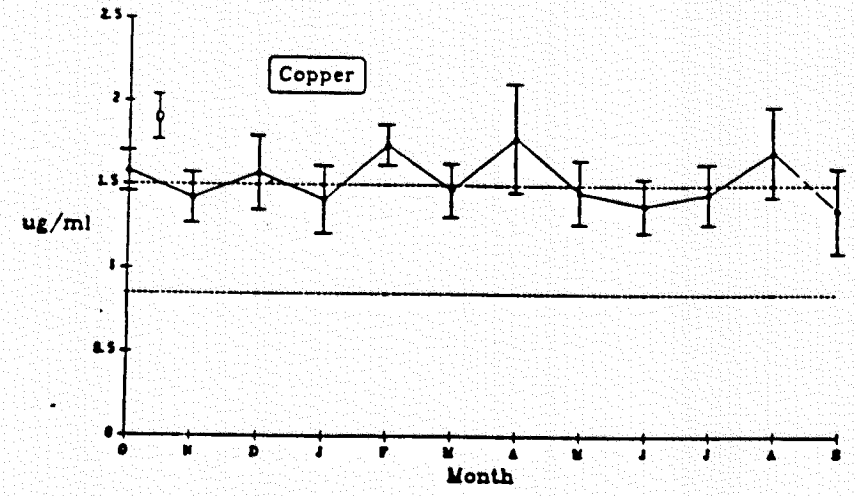

FIG. 5. Plasma levels of copper in patients on HPN. Data presented are as described in Figure 1.

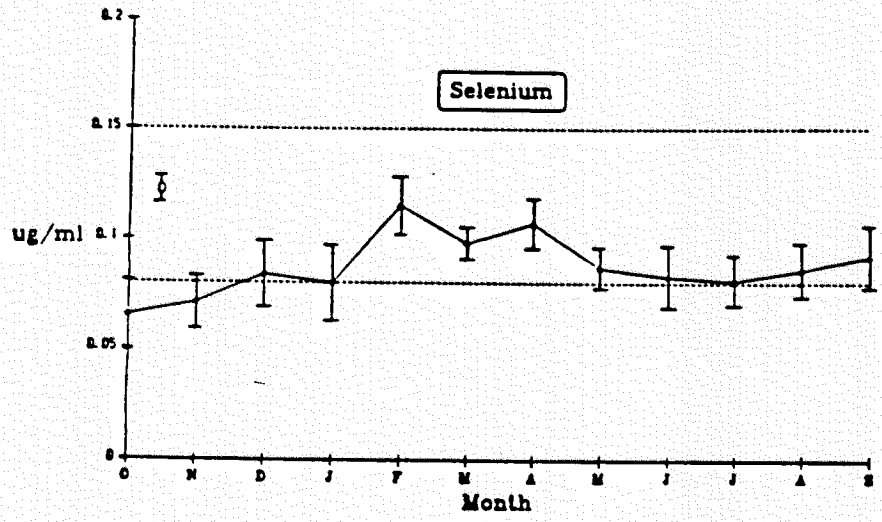

FIG. 6. Plasma levels of selenium in patients on HPN. Data presented are as described in Figure 1.

ing survival after small bowel resection is dependent on the use of HPN.

Initial problems with HPN were similar to those found in the hospital, such as sepsis, clotted catheter, and venous thrombosis.[19] These problems, for the most part, have been controlled through training, proper technique, and adequate surveillance. However, as the population of HPN patients grew, unusual nutrient deficiencies began to appear. Deficiencies of molybdenum,[20] selenium,[9] and biotin,[21] virtually unheard of in the general population, have developed in patients on long-term parenteral nutrition for 12–24 months.

In the present study, plasma concentrations of the fat-soluble vitamins A, E, and 1,25-dihydroxyvitamin D, as well as the micronutrients selenium, zinc, and copper, were measured in eight patients who had been on HPN for 1–92 months. Although all of the individuals had oral intake during the study, their ability to absorb nutrients internally was seriously limited due to various surgical procedures.

Vitamin A and E levels in HPN patients have been previously studied by Shils et al.[22] At levels of vitamin A and E supplementation similar to those used in our study, their patients maintained mean plasma vitamin A levels near the top of the normal range, whereas vitamin E levels were maintained in the lower end of the normal range. In their study, however, vitamins were not infused for at least 36 hr prior to drawing blood for analysis, whereas in the present study, the time period was at least 8 hr. In our study, it is apparent that the patients did not have a vitamin A or E deficiency. Indeed, the vitamin E levels were above normal, and the increase over time on HPN can be described by linear regression. The first 7 months of the study were marked by rather large fluctuations in plasma vitamin E concentrations. As these fluctuations were not noted for the other two fat-soluble vitamins measured, and there was no change in the level of vitamin supplementation, the reasons for the variability are unknown. It is interesting that the patients who showed the greatest variability over the first 7 months also had been on HPN longer than the other subjects in the study (56 and 92 months). It is possible that the variability was due to tocopherol in the iv fat solution. However, as all patients received iv fat, and only two demonstrated great variability, this does not seem likely.

There has been great interest and controversy regarding the role of vitamin D and vitamin D metabolites in the etiology of metabolic bone disease. This syndrome, first described by Shike et al[13] and Klein et al,[14] was most recently described in a patient who had received TPN for 6 months.[23] In all of these reports, removal of vitamin D from the TPN solutions resolved the symptomatology. In one study,[14] 1,25-dihydroxyvitamin D levels were depressed in patients receiving parenteral vitamin D. These levels rebounded to the low normal range after vitamin D supplementation was discontinued. However, the relationship between metabolic bone disease and vitamin D supplementation in HPN patients has been unclear.[24]

At no time during the 12-month period did any of our patients develop symptoms consistent with metabolic bone disease, and plasma values for 1,25-dihydroxyvitamin D remained comfortably within the normal range. These results suggest that vitamin D supplementation in HPN does not affect the development of metabolic bone disease.

It is well accepted that zinc and copper additives are required in TPN, and reports of zinc deficiency[8] and copper deficiency[11] in long-term TPN can be traced to insufficient supplementation. The zinc supplementation in this study was 5 mg/day. The RDA is 15 mg/day, which was set assuming a 33% absorption rate. Similarly, copper supplementation in this study was 1 mg/day, whereas the requirement has been set at 2–3 mg/day. The requirement was set assuming a 33% absorption rate. It is not clear how different states of disease affect these requirements. The AMA has suggested that TPN solutions be supplemented with zinc at 2.5–4.0 mg/day in stable adults (with an additional 2.0 mg/day for the catabolic state) and copper at 0.5–1.5 mg/day.[25] We followed these guidelines when establishing the standard zinc and copper additives, and found the HPN patients in this study to be adequately supplemented. The control values for copper fell outside the normal range. This appears to have been due to a dichotomy between the mean values for the males *vs* the females (1.29 *vs* 2.55 μg copper/ml plasma, respectively). Although not documented for this study, it was demonstrated previously that oral contraceptives cause a significant increase in serum copper,[26,27] and this effect may have been responsible for the elevated plasma copper values for the control females.

The role of selenium in HPN has generated much interest recently. Two reports[28,29] have noted significantly depressed selenium levels in HPN patients relative to controls. Similarly, mean patient plasma selenium concentrations remained in the low-normal to below-normal range for most of this study. At the start of the study, no patients were receiving selenium supplementation. However, one patient who had been on HPN for 92 months before the start of this study developed muscle pain and weakness. At that time, her plasma selenium concentration was in the low-normal to below-normal range. She began receiving selenium supplementations in late May, and for the final 4 months, her plasma selenium concentration rose to 0.119 ± 0.008 and her symptoms resolved. Based on these results, two other patients with low-average selenium concentrations (0.067 ± 0.015 and 0.065 ± 0.021 μg/ml) recently have begun selenium supplementation at 120 μg/day. The NRC has listed a safe and adequate intake of selenium of 50–200 μg/day for adults.[30]

It appears that the described HPN regimen of fat-soluble vitamin and mineral supplementation maintains adequate plasma levels for all of the nutrients except selenium. In addition, no signs of metabolic bone disease were found. Selenium levels in patients on HPN should be monitored regularly, and supplementation may be necessary if clinical conditions warrant.

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REFERENCES

1. Dudrick SJ, Wilmore DW, Vars HM, et al: Long-term parenteral nutrition with growth development and positive nitrogen balance. Surgery 64:134–142, 1968
2. Dudrick SJ, Wilmore DW, Vars HM, et al: Can intravenous feeding as the sole means of nutrition support weight loss in an adult? Ann Surg 169:974–984, 1969
3. Tsallas G, Baun DC: Home care total parenteral alimentation. J Hosp Pharmacol 29:840–846, 1972
4. Langer B, McHattie JD, Zohrab WJ, et al: Prolonged survival after complete small bowel resection using intravenous alimentation at home. J Surg Res 15:226–233, 1973
5. McGill DB, Jeejeebhoy KN: Long-term parenteral nutrition. Gastroenterology 67:195–197, 1974
6. Broviac JW, Scriber BH: Prolonged parenteral nutrition in the home. Surg Gynecol Obstet 139:24–28, 1974
7. Jeejeebhoy KN, Langer B, Tsallas G, et al: Total parenteral nutrition at home: Studies in patients surviving 4 months to 5 years. Gastroenterology 71:943–953, 1976
8. Kay RG, Tasman-Jones C, Pybus J, et al: Acute zinc deficiency in man during intravenous alimentation. Ann Surg 183:331–340, 1976
9. vanRij AM, Thomson CD, McKenzie JM, et al: Selenium deficiency in total parenteral nutrition. Am J Clin Nutr 32:2076–2085, 1979
10. Howard L, Chu R, Femen S, et al: Vitamin A deficiency from long-term parenteral nutrition. Ann Intern Med 93:576–577, 1980
11. Karpel JT, Peden VH: Copper deficiency in long-term parenteral nutrition. J Pediatr 80:32–36, 1972
12. Howard L, Ovesen L, Satya-Murti S, et al: Reversible neurological symptoms caused by vitamin E deficiency in a patient with short bowel syndrome. Am J Clin Nutr 36:1243–1249, 1982
13. Shike M, Sturtridge WC, Tam CS, et al: A possible role of vitamin D in the genesis of parenteral nutrition-induced metabolic bone disease. Ann Intern Med 95:560–568, 1981
14. Klein FL, Horst RL, Norman AW, et al: Reduced serum levels of 1,25-dihydroxyvitamin D during long-term parenteral nutrition. Ann Intern Med 94:638–643, 1981
15. Bieri JG, Tolliver TJ, Catignani GL: Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. Am J Clin Nutr 32:2143–2149, 1979
16. Steel RGD, Torrie JH: Principles and Procedures of Statistics, 2nd ed. McGraw-Hill, New York, 1980
17. Federer W, Zelen M: Analysis of multifactor classifications with unequal numbers of observations. Biometrics 22:525–552, 1966
18. Baumgartner TG: Clinical Guide to Parenteral Nutrition. Educational Publications, Melrose Park, IL, 1984
19. Dudrick SJ, O'Donnell JJ, Englert DM, et al: 100 patient years of

ambulatory home parenteral nutrition. Ann Surg 199:770–781, 1984
20. Abumrad NN, Schneider AJ, Steele D, et al: Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy. Am J Clin Nutr 34:2551–2559, 1981
21. Mock DM, Baswell DL, Baker H, et al: Biotin deficiency complicating parenteral alimentation: Diagnosis, metabolic repercussions, and treatment. J Pediatr 106:762–769, 1985
22. Shils ME, Baker H, Frank O: Blood vitamin levels of long-term adult home parenteral nutrition patients: The efficiency of the AMA-FDA parenteral multivitamin formulation. JPEN 9:179–188, 1985
23. Seligman JV, Basi SS, Deitel M, et al: Metabolic bone disease in a patient on long-term total parenteral nutrition: A case report with review of literature. JPEN 8:722–727, 1984
24. DeLuca HF: Metabolic bone disease in long-term parenteral nutrition (Letter). JPEN 9:71, 1985
25. American Medical Association: Guidelines for essential trace element preparations for parenteral use. JAMA 241:2051–2054, 1979
26. Schenker JG: Serum copper and ceruloplasmin levels in women taking oral contraceptives. IN Proceedings of the 3rd International Symposium on Trace Element Metabolism in Man and Animals-3. Kirchgessner M (ed). Arbeitskreis für Tierernährungs forschung, freising-Weihenstephan, 1978, pp 374–377
27. Vir SC, Love AHG: Zinc and copper nutriture of women taking oral contraceptive agents. Am J Clin Nutr 34:1479–1483, 1981
28. Fleming CR, McCall JT, O'Brien JF, et al: Selenium status in patients receiving home parenteral nutrition. JPEN 8:258–262, 1984
29. Baptista RJ, Bistrian BR, Blackburn GL, et al: Suboptimal selenium status in home parenteral nutrition patients with small bowel resections. JPEN 8:542–545, 1984
30. National Research Council: Recommended Dietary Allowances, 9th ed. National Academy of Sciences, Washington, DC, 1980
31. Whetter PA, Ullrey DE: Improved fluorometric method for determining selenium. J Assoc Official Anal Chem 61:927–930, 1978

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INTRALIPID

Blood Vitamin Levels of Long-Term Adult Home Total Parenteral Nutrition Patients: The Efficacy of the AMA-FDA Parenteral Multivitamin Formulation

MAURICE E. SHILS, M.D., SC.D.,* HERMAN BAKER, PH.D.,† AND OSCAR FRANK, PH.D.‡

*From the Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, *Department of Medicine, Cornell University Medical College, New York, New York; †Departments of Medicine and Preventive Medicine/Community Health, and ‡Department of Medicine, University of Medicine and Dentistry of New Jersey, Newark, New Jersey*

ABSTRACT. Although the AMA-FDA parenteral adult multivitamin formula is now widely used, there are no published data on the efficacy of this formulation in maintaining adequate vitamin nutriture in patients on long-term parenteral nutrition. Blood levels of its constituent nutrients were determined in 16 clinically stable home total parenteral nutrition patients with severe gastrointestinal dysfunction, the majority of whom had been on home total parenteral nutrition for 1 to 9 yr and most of whom were ingesting some food orally. The daily formula (MVI-12) was added to the basic total parenteral nutrition formula in 2-day batches; the vitamins were thus infused approximately 3 hr after preparation on day 1 and after 27 hr on day 2. The duration of infusions was from 8 to 16 hr. Blood was drawn approximately 36 hr after completion of the last vitamin infusion. Plasma, trichloroacetic acid-treated plasma, and whole blood were frozen until analyzed for the vitamins by microbiologic or chemical methods. All vitamin levels, except for vitamin D metabolites, were measured four times in each patient between the 4th and 36th wk while receiving daily MVI-12. Single determinations of 25-OH and 1:25 $(OH)_2$ vitamin D were made in eight of the 16 patients between the 61st and 84th wk while on MVI-12. Repeat values during this extended period were also made on five of the patients for vitamins A and E. These values were compared with serum vitamin levels obtained on an earlier formulation (MVI concentrate, Berocca C, and folate each given twice weekly and B_{12} given once weekly). The AMA-FDA formula given daily maintained blood levels above the lower normal limits for most of its constituent vitamins and vitamin D metabolites for the great majority of stable home total parenteral nutrition adults with unexplained occasional exceptions. However, almost half of the vitamin A levels and some of the pantothenate and biotin values were above the normal range; these tended to be associated with the presence of renal disease. Ascorbic acid and thiamin levels tended to be clustered in the lower normal range. Because of evidence for loss of ascorbic acid standing in total parenteral nutrition solutions for 24 hr prior to infusion, it is recommended that the vitamin formulation be added to the total parenteral nutrition solution just prior to infusion. (*Journal of Parenteral and Enteral Nutrition* 9:179–188, 1985)

In July 1979 the FDA approved a new adult parenteral vitamin formulation[1] based on the recommendations of the Nutrition Advisory Group of the American Medical Association and hence designated the AMA-FDA formulation.[2,3] Since that time various pharmaceutical companies have issued formulations which follow the FDA guidelines. To date no published data are available on the ability of these formulations to maintain normal blood values in long-term total parenteral nutrition (TPN) patients.

This report summarizes observations made periodically over 5 to 8 months of vitamin levels in 16 long-term stable home TPN (HTPN) patients with severe malabsorption or intestinal obstruction who were given an AMA-FDA formulation. (MVI-12, USV Laboratories, Tuckahoe, NY).

MATERIALS AND METHODS

Patients

Clinical data on participating patients are given in Table I. There were eight of each sex with ages ranging from 21 to 70 yr. Six patients had been on long-term HTPN for periods of 3 to 9 yr, five from 1 to 3 yr, and four for 7 to 12 months prior to initiating the AMA-FDA formula. The serious degree of malabsorption of most of the subjects is indicated by their severely impaired xylose excretion with the lower limit of normal being more than 4.2 g in 5 hr (Table I). Excluded from the study were patients with known active or suspected cancer as were those on maintenance chemotherapy and those requiring home parenteral alimentation primarily to meet requirements for large amounts of fluid and electrolytes.

All patients entered in the study and previously signed consent forms for participation in the study. The study was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki. All were in good nutritional state, afebrile, at a satisfactory weight for height, clinically stable, and fully ambulatory and active. Most ate a variety of foods *ad libitum* (despite the attendant diarrhea) but with voluntary restriction in all but a few cases. Since almost all patients were at risk of renal oxalate stone formation because of resected ileum and the presence of most of their colon, restriction had been advised of oxalate containing fruits and vegetables and of fat. The individual averages for caloric intake in the TPN solutions and by mouth are given in Table I.

No oral vitamin supplements were taken for at least 1

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Reprint requests to: Dr. Maurice E. Shils, Director of Clinical Nutrition, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

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TABLE I

Data on study patients

Pt/Age/Sex	TPN duration (mo)[a]	Diagnosis	Wt (kg)	Xylose Test[b] (5-hr urine) (g)	Avg Daily Caloric Intake in TPN (kcal)	Oral (kcal)
V/61/F	9	Ovarian carcinoma, s/p resection and radiation; radiation enteritis, persistent small bowel fistula; NED,[c] renal dysfunction, moderate	57.0	0.29	2102	690
MAC/38/F	12	Crohn's disease, s/p massive bowel resection	89.3	1.88	1500	Variable (1000-2360)
LAN/69/F	7	Mesenteric artery occlusion with bowel infarction; s/p massive bowel resection	58.5		1391	1460
BOR/25/M	16	Embryonal rhabdomyosarcoma; s/p resection, radiation, chemotherapy; radiation enteritis, NED, renal dysfunction, mild	58.5	0.71	2313	1400
FIS/34/M	1	Mesenteric artery occlusion with bowel infarction; s/p massive bowel resection; renal dysfunction moderate	62.7	0.45	2238	2300
BI/49/F	36	Mesenteric artery occlusion with bowel infarction; s/p massive bowel resection; diabetes,[d] renal dysfunction, mild	63.0		1643	Variable (200-1340)
LAU/45/F	26	Lymphoma; s/p massive bowel resection and radiation therapy; NED	57.4	0.60	2159	0
WIT/31/M	66	Crohn's disease; s/p bowel resection[e]	74.5	3.3	1854	1140
CAS/44/M	46	Intestinal pseudoobstruction[f]	67.2		2264	480
MEL/66/M	43	Mesenteric artery occlusion; s/p massive small bowel resection; renal dysfunction, severe[g]	74.4	0.15	1038	850
CAP/21/M	22	Embryonal rhabdomyosarcoma; s/p chemotherapy bowel resection; radiation enteritis; NED[c,e] renal dysfunction, mild	57.2	1.38	1889	400
ACA/66/F	10	Gastric leiomyosarcoma; s/p subtotal gastrectomy, chemotherapy and radiation therapy; radiation enteritis; NED	54.0	1.35	1413	460
DEU/52/M	91	Testicular carcinoma; s/p orchiectomy, node dissection and abdominal radiation therapy; radiation enteritis with bowel obstruction; NED; renal dysfunction, moderate[d]	65.0	0.8	1654	<100
IER/63/F	34	Mesenteric artery occlusion with bowel infarction; s/p massive bowel resection	58.0	0.53	1276	1040
VAN/26/M	40	Crohn's disease; s/p massive bowel resection; renal dysfunction, mild	74.5		1563	1670
ZOC/70/F	8	Endometrial carcinoma; s/p resection and radiation; radiation enteritis with bowel resection; NED	60.0	0.85	1350	350

[a] To 4/1/81, the mean date of starting the AMA-FDA formulation (MVI-12).
[b] Lower limit of normal 4.2 g.
[c] No evidence of recurrent malignancy.
[d] Oral medication: vitamin E 50 mg until shortly after the 2nd sampling on MVI-12.
[e] Oral medications: urecholine and metoclopromide.
[f] Oral medications: allopurinol and furosemide.
[g] Oral medications: methadone.

month prior to and during the study excepting vitamin E which had been ingested by five of the patients at 50 mg/day. This preparation was discontinued in July 1981 approximately 3 months after starting the AMA-FDA formula. Oral medications taken on a regular basis during the study are indicated in Table I.

Intravenous Solutions

These were prepared by the patient or family member in 2-day batches at home with the exception of one patient whose formula was made in the hospital. The basic ingredients were placed into 2- or 3-liter PVC bags. The TPN formulas included Aminosyn 10% at 750 to 1000 ml/day, glucose as the major source of calories and Intralipid (10%) 500 ml twice weekly given by piggy-back infusion to supply essential fatty acids and some calories and tocopherol. Sodium, potassium, chloride, magnesium, phosphate, and zinc were given daily in amounts sufficient to maintain normal serum levels. Calcium gluconate (10%) was given daily in amounts varying from 276 to 552 mg/day. Copper, manganese, and chromium salts were given twice weekly. Total daily intravenous fluid volume varied from 2 to 5 liters depending on intestinal fluid losses. The solution was refrigerated from the completion of preparation until infusion was started.

The TPN was infused at night into a central venous catheter through an 0.44-μ filter for periods varying from 8 to 16 hr with the majority receiving the infusion in 8 to 12 hr. On completion of the infusion, dilute heparin solution was injected into the central venous catheter which was then closed with a sterile cap.

Prior to the AMA-FDA formula the patients had received multiple preparations designed to provide all of the vitamins. MVI concentrate (5 ml) was given on Tuesday and Friday; injectable Berocca C (2 ml) on Thursday and Saturday; folate (1.5 mg each) on Wednesday and Saturday; vitamin B_{12} (50 μg) on Wednesday, and vitamin K_1 oxide (5 mg) as Aquamephyton every Monday. The average daily intakes are given in Table II.

The AMA-FDA formulation was given on a daily basis (Table II) throughout the study except when sampling of blood was to be done for the vitamin determinations (*vide infra*). The TPN solutions were prepared on a 2-day basis; hence, the elapsed time from the addition of the vitamin solution to the TPN formula to the beginning of the infusion was approximately 3 hr on the day of TPN preparation and 27 hr on the 2nd day. Five milligrams of vitamin K_1 oxide were given every Monday. To preserve thiamin against the destructive effect of sodium bisulfite present in the amino acid solution, the patients were instructed to add the vitamins to the other solutions in the TPN bag and add the Aminosyn 10% last, thus minimizing the bisulfite concentration.

Vitamin Infusion Prior to Sampling

The protocol required that vitamins were not to be infused for at least 36 hr prior to drawing blood for vitamin analysis other than for vitamin D metabolites. Thus the AMA-FDA formulation was omitted from the TPN solution infused Tuesday night, the infusion terminated at 7 AM and blood drawn 3 to 4 hr later. The intermittent nature of addition of the various components of the previous vitamin formulation (*vide supra*) resulted in the lapse of 7 days for vitamin B_{12}, 4 days for MVI, and 3 days for Berocca C and folate between their infusion and sampling.

TABLE II
Vitamins provided in two vitamin formulations[a]

Vitamin	Original vitamin formula	AMA-FDA Formula (MVI-12)[b]	
	Label	Label	Analysis
Retinol (IU)	2856[c]	2300	4950
Ergocalciferol (IU)	286[c]	200	
dl-α-tocopherol acetate (IU)	1.4[c,d]	10	14.5
Ascorbic acid (mg)	171[c,e]	100	126
Thiamin HCl (mg)	17[c,e]	3	3
Riboflavin (as PO_4) (mg)	5.7[c,e]	3.6	3.9
Niacinamide (mg)	51[c,e]	40	40
Pyridoxine HCl (mg)	10[c,e]	4	7.6
Panthenol (mg)	13[c,e]	15	
Biotin (μg)	57[c]	60	57.8
Folic acid (μg)	430[f]	400	390
Vitamin B_{12} (μg)	7[f]	5	5

[a] Vitamin K_1 oxide (Aquamephyton): 5 mg added once weekly in both formulations.
[b] Present in each day's TPN.
[c] From MVI concentrate given twice weekly. Each 5 ml is labeled to contain: vitamin A 10,000 IU, D_3 1000 IU, E 5 IU, thiamin 50 mg, riboflavin 10 mg, niacinamide 100 mg, pyridoxine 15 mg, panthenol 25 mg, ascorbic acid 500 mg.
[d] Plus an estimated average daily intake from 500 ml of 10% Intralipid (twice weekly) of 1.7 mg α-tocopherol and 4 mg of other tocopherols.
[e] From Berocca C injectable (given twice weekly). Each 2 ml is labeled to contain: thiamin HCl 10 mg, riboflavin 10 mg, niacinamide 80 mg, pyridoxine HCl 20 mg, panthenol 20 mg, *d*-biotin 200 μg, ascorbic acid 100 mg.
[f] 1.5 mg folate in TPN twice weekly; 50 μg of vitamin B_{12} in TPN once weekly.

Actual analytic findings on a sample of MVI-12 are given in Table II. It is apparent that there were significant overages for most of the vitamins as the result of manufacturing practices.

Blood samples were obtained for vitamin analyses four times in the course of the study. In all but a few patients sampling was clustered at 4 to 7, 11 to 14, 18 to 23, and 28 to 35 wk. Vitamins A and C were also determined in subjects after a period of 430 to 571 days on MVI-12. A single sampling for 25-OH vitamin D, 1:25 $(OH)_2$ vitamin D, and parathyroid hormone was performed on eight of the 16 patients who had been on MVI-12 continuously for an average of 507 days (range 430–588). MVI-12 was present in the TPN solution at the time of the sampling for this metabolite and blood was drawn as infusion of the TPN solution was terminating.

Sampling

Blood for vitamin analyses was drawn from an anticubital vein and placed immediately into three 10-ml vacutainer tubes containing small amounts of disodium edetate. One tube of whole blood was transferred within 1 hr to a plastic tube which was sealed and frozen while the contents of the other two tubes were centrifuged and the plasma removed. Two milliliters of plasma were

added to 6 ml of 5% trichloroacetic acid, the tube shaken gently, centrifuged, and the supernate removed and frozen in plastic tubes. The remaining plasma was frozen in sealed plastic tubes. Serum for 25-OH vitamin D was frozen until thawed for analysis.

Vitamin assays were performed at the New Jersey Medical School. Whole blood was assayed for thiamin[4] and biotin[5] using *Ochromonas danica* (ATCC no. 30004); nicotinate,[6] pantothenate[7] and riboflavin[8] were analyzed using *Tetrahymena thermophila* (ATC no. 30008). This latter protozoan was used for assaying plasma vitamin B_6.[9] Plasma vitamin B_{12}[10,11] was analyzed with *Ochromonas malhamensis* and *Lactobacillus casei* (ATCC no. 7469) was used to assay for folates.[11,12] Vitamins A, E, C, and carotenes were determined chemically in plasma.[11] Analyses for 25-OH vitamin D metabolites (total of D_2 and D_3) in serum were performed in the laboratory of Dr. Michael Horlick at Massachusetts General Hospital. Initial separation and purification[13] was followed by a competitive protein binding analysis.[14]

The range of normal values for the vitamins other than the vitamin D metabolites was obtained in previous studies of 234 free-living healthy males and females between ages of 20 and 50 yr ingesting mixed diets by mouth.[11] The ranges indicated in the figures represent 95% confidence limits in a log normal distribution.

RESULTS

The vitamin levels obtained at each sampling for each patient are plotted in Figures 1 to 11 together with means and SDs. The significance (p values) of the differences (p values as determined by Student's t-test)[15] from the means for each period of the AMA-FDA formula are indicated in comparison with the values obtained with the previous vitamin formulation.

Vitamin A

As with most vitamins a wide range of individual values was observed at each sampling period but all values were above the minimal normal value of 25 μg/dl with both formulations (Fig. 1). With MVI-12 the mean values at each sampling period were near or above the upper limit of normal with 23 of 57 determinations being above 100 μg/dl. Five of the seven patients with persistent high values had moderate to serious renal impairment (see "Discussion"). When analyses were repeated on five of the study patients in a period of 430 to 571 days after initiating MVI-12, the mean value was 60 μg/dl; with the range being 32 to 103. Indicative of the severe malabsorption and the tendency of most patients to eat sparingly of green leafy and yellow vegetables was the observation that plasma carotene was extremely low or barely detectable in almost all subjects; these data are omitted.

Vitamin E

The average daily intake on the previous formula was 1.4 mg/day plus an estimated additional provision of 1.7 mg of α-tocopherol when Intralipid was infused twice

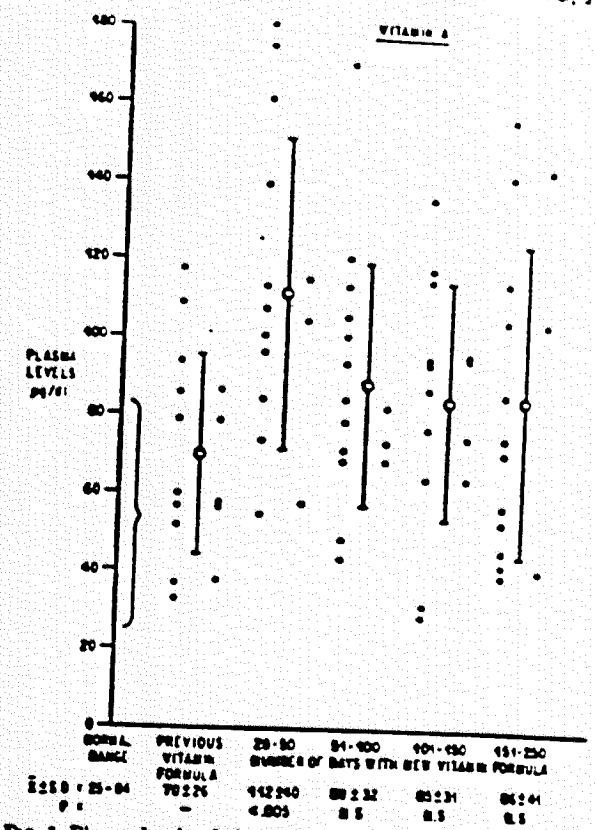

FIG. 1. Plasma levels of vitamin A in subjects on long-term HTPN in the course of daily administration of adult AMA-FDA multivitamin parenteral formulation (MVI-12). The normal range is indicated along the *ordinate*. Individual patient values are indicated by *closed dots*, the mean and 1 SD limits are indicated by an *open circle* and *vertical lines*. The first set of data was obtained while the subjects were on another multivitamin formula (designated as previous vitamin formula) utilized prior to the adult AMA-FDA formula which included MVI, Berocca C, folate, and B_{12} given intermittently each week (*cf* Table II). The subsequent data were obtained periodically after the MVI-12 was instituted. The p values compare the values obtained at each sampling on MVI-12 with those obtained on the previous vitamin formulation.

weekly (Table II). This intake was reflected in five borderline low values and four subnormal levels (Fig 2). It is of interest that the three lowest values were in patients who often failed to take fat at that time because of alleged unpleasant side-effects (metallic taste, unpleasant body odor). With the AMA-FDA formulation the values returned to the normal range by its third sampling in all but one patient. The exceptional patient was one who was the least compliant and whom we know refused to infuse Intralipid on a regular basis and who was ingesting the drugs metaclopromide and urecholine orally as symptomatic treatment of his pseudointestinal obstruction. This patient continued to have low values as indicated by a plasma level of 0.3 at 539 days on MVI-12. Five of these patients sampled during a period 430 to 571 days on MVI-12 had an avearge E value of 0.92 mg/dl (range 0.5–1.2). As noted in the "Discussion," these patients have low cholesterol and triglyceride levels which may be associated with decreased plasma E level.[16]

As noted earlier five patients were given 50 mg of mixed tocopherols orally until shortly after the second sampling on the MVI-12. Comparison of their vitamin

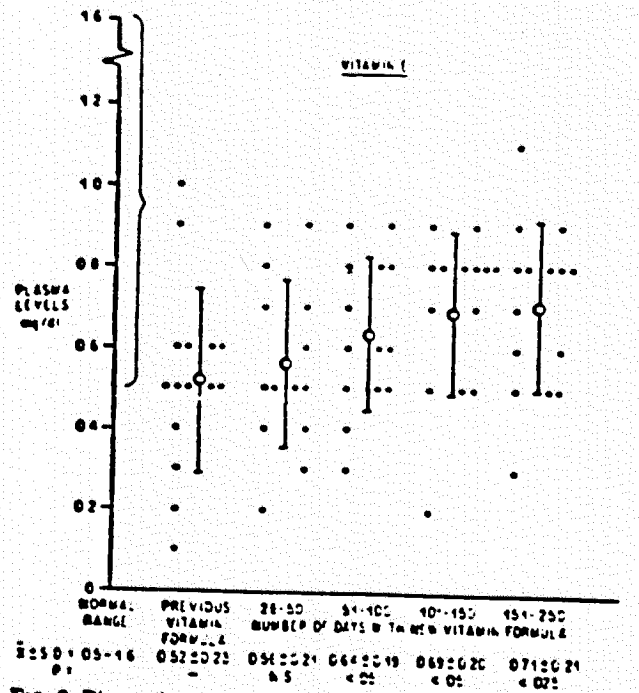

FIG. 2. Plasma levels of vitamin E in subjects on long-term HTPN in the course of administration of the adult AMA-FDA multivitamin parenteral formulation (MVI-12). See the legend of Figure 1 for description of data presentation.

levels on the original vitamin formulation and over the first two periods on MVI-12 indicate no difference in their mean values with seven patients over the same period who received no oral vitamin E supplement and who continued to infuse Intralipid on a regular basis suggesting impaired oral absorption.

Vitamin K

This is not a component of the adult AMA-FDA formula; 5 mg were added to TPN once weekly. Prothrombin and partial thromboplastin times were determined periodically throughout the study and were consistently within normal levels in all subjects.

Vitamin D Metabolites

25-OH-vitamin D in the eight patients sampled averaged 22.3 ng/ml with the range being 11 to 36; the normal range is 8 to 55 ng/ml.[13] 1:25 Dihydroxy vitamin D in the eight patients averaged 59.1 (range 46–87); the normal range is 26 to 65 pg/ml. Parathyroid hormone values were normal.

Ascorbic acid (Fig. 3)

In the previous vitamin formulation this vitamin as well as other water-soluble vitamins, with the exceptions of folate, biotin and B_{12}, were infused four times weekly in the forms of MVI and Berocca C (Table II). This vitamin was provided daily in the AMA-FDA formulation. Appreciable variability in vitamin C levels was noted at each sampling. The mean values were above the lower limit of normal at each sampling with a slight but not significant decline in mean values noted at the last sampling on MVI-12. There were eight values with this formulation in the range of 0.1 to 0.2 mg/dl; seven of these low values occurred in two patients. While other subjects had levels transiently below 0.4, none was consistently below this value. The patient with consistently low E values noted above was one of the two with low C values. The tendency to values in the lower normal range or below led to a change in the time of addition to vitamins to TPN (*vide infra*).

Thiamin

The marked reduction in average daily thiamin content between the previous formula and the AMA-FDA formula (Table II) was associated witht a general decline in plasma levels with MVI-12 (Fig. 4). Nevertheless the values remained within the normal range except for a transiently low value in one patient.

Vitamin B_6 and Niacin

As indicated in Figures 5 and 6, there were two or three patients with values below normal for these vitamins while receiving the previous formulation. With MVI-12 there were occasional low values at the first two samplings; thereafter all patients were within the normal range.

Riboflavin (Fig. 7), biotin (Fig. 8), vitamin B_{12} (Fig. 9), and pantothenate (as panthenol) (Fig. 10) were in-

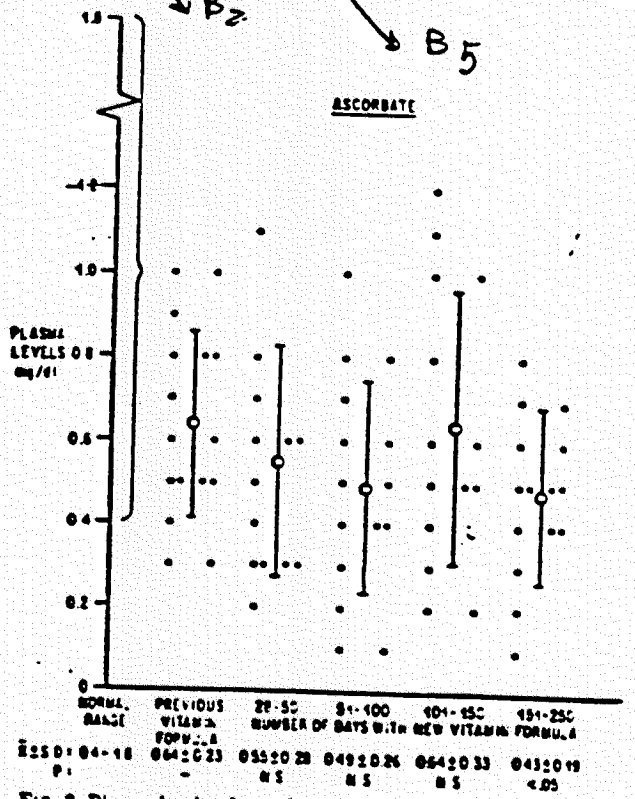

FIG. 3. Plasma levels of ascorbate in subjects on long-term HTPN in the course of administration of the adult AMA-FDA multivitamin formulation (MVI-12). See the legend of Figure 1 for description of data presentation.